Differences in Adverse Drug Events Among Pediatric Patients With and Without Cancer: Sub-Analysis of a Retrospective Cohort Study

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ORIGINAL RESEARCH ARTICLE

Differences in Adverse Drug Events Among Pediatric Patients With and Without Cancer: Sub-Analysis of a Retrospective Cohort Study

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Abstract

Objectives This study investigated the differences in the incidence and severity of adverse drug events (ADEs) in pediatric patients with and without cancer.

Methods We used data from the Japan Adverse Drug Events Study for pediatrics, a cohort study enrolling pediatric inpatients at two tertiary care teaching hospitals in Japan. ADEs were identified by on-site review of all medical charts, incident reports, and prescription queries by pharmacists. Two independent physicians reviewed all potential ADEs and classified ADEs in terms of severity and class of causative medication. We compared the incidence and characteristics of ADEs between pediatric cancer patients and non-cancer patients.

Results We enrolled 1189 patients during the study period, 27 with cancer and 1162 without cancer. We identified 480 ADEs in 234 patients (20%): 191 ADEs among 21 cancer patients and 289 ADEs among 213 non-cancer patients (7.1 per patient vs. 0.25 per patient, respectively; $p < 0.0001$). The most common medications associated with ADEs in cancer patients were antitumor agents; in contrast, medications associated with fatal or life-threatening ADEs in cancer patients were most often sedatives (25%) and blood products (25%). Medications associated with fatal or life-threatening ADEs among non-cancer patients were most often sedatives (15%). The percentages of fatal or life-threatening ADEs in cancer patients and non-cancer patients were 2.1 and 4.5%, respectively.

Conclusions Pediatric patients with cancer have a higher risk for ADEs. Although the overall severity was similar between patients with and without cancer, the most common classes of causative medication and medications associated with a higher rate of severe ADEs differed. Application of this information may help minimize the impact of ADEs in pediatric patients.

Key Points

Adverse drug events occurred in pediatric patients with cancer 28 times more frequently than in those without cancer.

As expected, the medications most commonly associated with adverse drug events in pediatric patients with cancer were antitumor agents, but fatal or life-threatening events due to such medications were rare (0.7%).

The category of causative medication and severity of adverse drug events differed between pediatric patients with cancer and without cancer.

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1 Introduction

Adverse drug events (ADEs) are injuries due to medication use. ADEs represent a serious problem in healthcare because they are the most frequent cause of injuries due to medical care in hospitals in developed countries [1, 2]. In Japan, the JADE (Japan Adverse Drug Events) study, a multicenter cohort study, was conducted to estimate the epidemiology of ADEs in several settings [3]. In both Japan and in Western countries, ADEs have been associated with substantial increases in morbidity and mortality [1, 3–5]. Patients who need chemotherapy often experience ADEs as the result of antitumor agents [6]. Pediatric inpatients are vulnerable to ADEs because they often cannot describe their symptoms and have small metabolic reserves [7, 8]. In particular, pediatric cancer patients receiving antitumor agents are at high risk for ADEs because of the nature of the patients and drugs involved [9, 10].

To examine the epidemiology of ADEs in pediatric inpatients, we conducted the JADE study for pediatric patients [11]. As a sub-study, we analyzed differences in ADEs between pediatric patients with and without cancer and evaluated the causes, symptoms, and severity of the ADEs.

2 Methods

2.1 Study Design and Patient Population

This study was based on the data from the JADE study for pediatric inpatients, which was a historical cohort study performed in two tertiary care teaching hospitals in Japan. The details of the study have been described elsewhere [11]. Briefly, we included all patients aged ≤15 years admitted to any ward, including the neonatal intensive care unit (NICU) and pediatric intensive care unit (ICU), and patients aged >15 years admitted to any pediatric ward over a 3-month period in 2009. Because some adult patients with congenital or metabolic diseases were cared for by pediatricians from a young age, such patients were included in this cohort study based on the protocol. We excluded neonates in well-baby nurseries from this study because they were healthy and not cared for by pediatricians. If neonates had a problem such as temporary dyspnea or mild cyanosis of the limbs at birth, they were admitted to the NICU and cared for by neonatologists. We included these neonates in this study. We categorized the age groups as follows: neonates (aged <1 month), infants (1 month to <1 year), preschoolers (1 year to <7 years), school-aged children (7 to <13 years), teenagers (13 to <19 years), and adults (≥19 years).

The institutional review boards of the two participating hospitals approved the study. Because all data were obtained as part of routine daily practice, the institutional review boards waived the need for informed consent.

2.2 Definitions

The primary outcome of the study was the occurrence of ADEs, which we compared between pediatric patients with and without cancer. Cancer patients were defined as those who were diagnosed with any malignant tumor or those who had a tumor and were receiving antitumor agents. Non-cancer patients included those with benign or other tumors. We used validated methodology for the classification of ADEs [12]. An ADE was defined as a health injury occurring because of medication use. For example, nausea or vomiting in a patient receiving an antitumor agent was considered an ADE. We categorized the severity of ADEs as follows: fatal (resulting in death), life-threatening (requiring transfer to the ICU or causing anaphylactic shock), serious (neutropenia requiring a special protective environment, cutaneous lesions requiring therapy, gastrointestinal bleeding, altered mental status, excessive sedation, increased creatinine level, or decreased blood pressure), or significant (rash, diarrhea, or nausea). Categories of ADE symptoms included bleeding; central nervous system; allergic or skin reaction; liver or metabolic dysfunction; cardiovascular; gastrointestinal; renal; respiratory; bone marrow suppression or cytopenia; and other.

We categorized medications as follows: antihistamines, antibiotics, antitumor agents, adrenaline/anticholinergics, blood products, hematopoietic drugs, anticoagulants, diuretics/cardiovascular agents, antipyretic analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, sedatives, antipsychotics, diagnostic drugs/electrolytes and fluids/others, antitussives, ophthalmic/otolaryngologic/dermatologic drugs, laxatives, local anesthetics, corticosteroids, hormones/insulin, aminophylline, and peptic ulcer drugs. Antitussives did not include codeine but did include expectorants, and sedatives did not include narcotics or opiates. Because doses for pediatric patients were generally determined by body weight, and the standard doses varied between drugs, we did not account for dose in the analyses.

2.3 Data Collection and Review Process

Trained reviewers based at each participating hospital reviewed all medical charts, laboratory results, incident reports, and prescription queries from pharmacists. The trained reviewers included a board-certified pediatrician,

pediatric nurses, and a dietitian; the pediatrician trained all reviewers in a standard manner, as reported elsewhere [12]. Reviewers collected the characteristics and administrative data for all patients enrolled in the cohort and identified potential ADEs and associated details, such as detailed symptoms and drug name, dose, route, and class.

After data collection, two independent physician reviewers assessed, in a standard manner, whether any potential ADEs should be classified as ADEs [12]. Briefly, the reviewers summarized and discussed many aspects, including preceding drugs, other causative conditions occurring during hospitalization, previous literature reports, alleviation after discontinuation of drug, repeated symptoms when the same drug was re-introduced, and so on. They classified the severity, symptoms, and class of medication involved in ADEs. When disagreement arose over classification of an event, the reviewers reached consensus through discussion. Uncertain symptoms or those for which consensus was not reached were excluded from the ADEs.

2.4 Statistical Analyses

Categorical variables regarding patient characteristics are reported as numbers and percentages. A Chi squared test was used to compare patients with and without cancer. We also constructed a logistic regression model for cancer patients who developed ADEs, adjusting for the age group and admission to an ICU. The likelihood of ADEs was expressed as an odds ratio (OR) and its 95% confidence interval (CI). The ADE rate per 100 patients, ADE severity, and ratio of ADE severity for each drug were compared between cancer and non-cancer patients; the Chi squared test was used for categorical variables.

We carried out all analyses using JMP 12.0 software (SAS Institute Inc., Cary, NC, USA). Two-tailed p values <0.05 were considered statistically significant.

3 Results

3.1 Patient Characteristics

Among the 1189 patients included in the JADE study for pediatrics, 480 ADEs occurred in 234 (20%) patients. Among the different age categories, there were 252 (21%) neonates, 174 (15%) infants, 465 (39%) preschoolers, 189 (16%) school-aged children, 98 (8%) teenagers, and 11 (1%) adults (Table 1). The age of adults ranged from 20 to 42 years.

Antibiotics (61%), antipyretic analgesics/NSAIDs (32%), adrenaline/anticholinergics (26%), and antitussives (26%) were the three most frequent classes of prescribed medication on admission.

3.2 Comparison of Cancer Patients and Non-Cancer Patients

In all, we included 27 cancer patients and 1162 non-cancer patients in this study. One patient with teratoma and another with optic glioma were categorized as cancer patients because they received chemotherapy during the hospitalization. Patients with cancer had more operations and received antitumor agents or anticoagulants more often than those without cancer (Table 1). On the other hand, patients without cancer more often received adrenaline/anticholinergics and antipyretic analgesics/NSAIDs. Overall, 191 ADEs occurred in 21 cancer patients and 289 ADEs occurred in 213 non-cancer patients. The ADE rate per 100 patients in cancer patients was 707 compared with 25 in non-cancer patients ($p < 0.0001$). The adjusted OR of ADEs among patients with cancer was 12.3 (95% CI 4.9–31.1) compared with patients without cancer.

The severity of ADEs in cancer patients was similar to that in non-cancer patients ($p = 0.13$). The percentages of fatal or life-threatening ADEs in cancer patients and non-cancer patients were 2.1 and 4.5%, respectively (Fig. 1).

Among 191 ADEs in cancer patients, 149 (78%) were associated with antitumor agents, 13 (7%) with corticosteroids, ten (5%) with antibiotics, and eight (4%) with sedatives. In contrast, among 289 ADEs in non-cancer patients, 135 (47%) were associated with antibiotics, 52 (18%) with sedatives, 21 (7%) with corticosteroids, and 13 (4%) with antipyretic analgesics/NSAIDs (Fig. 2).

In contrast to all ADEs, medications with a high frequency of fatal or life-threatening ADEs among cancer patients included sedatives (25%) and blood products (25%); those among non-cancer patients included anticoagulants (50%), sedatives (15.4%), and hormones/insulin (50%), although the sample size was small (Fig. 3).

3.3 Adverse Drug Events (ADEs) Due to Antitumor Agents

Among the 27 cancer patients, 149 ADEs occurred in 18 patients due to antitumor agents, for a rate of 552 per 100 patients. Analysis of the severity of ADEs due to antitumor agents showed there was one (0.7%) life-threatening ADE, 43 (29%) serious ADEs, and 105 (70%) significant ADEs. Symptom categories of ADEs due to antitumor agents included five (3%) bleeding, eight (5%) central nervous system, 11 (8%) allergic or skin reaction, 17 (11%) liver or metabolic dysfunction, one (0.7%) cardiovascular, 58 (39%) gastrointestinal, four (3%) renal, one (0.7%)

Table 1 Patient characteristics

Characteristics	All ($n = 1189$)	Cancer patients ($n = 27$)	Non-cancer patients ($n = 1162$)	p value
Age				
Neonate (<1 month)	252 (21)	0 (0)	252 (22)	0.02
Infant (1 month to <1 year)	174 (15)	5 (19)	169 (15)	
Preschooler (1 to <7 years)	465 (39)	12 (44)	453 (39)	
School-aged (7 to <13 years)	189 (16)	4 (15)	185 (16)	
Teenager (13 to <19 years)	98 (8)	6 (22)	92 (8)	
Adult (≥19 years)	11 (1)	0 (0)	11 (1)	
Sex				
Male	649 (55)	18 (67)	631 (54)	0.2
Surgery during hospitalization	294 (25)	14 (52)	280 (24)	0.001
Drug after admission				
Antihistamines	244 (21)	8 (30)	236 (20)	0.24
Antibiotics	727 (61)	19 (70)	708 (61)	0.32
Antitumor agents	4 (0.3)	3 (11)	1[a] (0.1)	<0.0001
Adrenaline/anticholinergics	309 (26)	1 (4)	308 (27)	0.006
Blood products	28 (2)	0 (0)	28 (2)	1.0
Hematopoietic drugs	24 (2)	0 (0)	24 (2)	1.0
Anticoagulants	86 (7)	6 (22)	80 (7)	0.002
Diuretics/cardiovascular agents	119 (10)	2 (7)	117 (10)	1.0
Antipyretic analgesics/NSAIDs	383 (32)	3 (11)	380 (33)	0.02
Anticonvulsants	173 (15)	7 (26)	166 (14)	0.09
Sedatives	69 (6)	4 (15)	65 (6)	0.07
Antipsychotics	13 (1)	0 (0)	13 (1)	1.0
Diagnostic drugs/electrolytes and fluids/others	967 (81)	21 (78)	946 (81)	0.63
Antitussives	305 (26)	3 (11)	302 (26)	0.12
Ophthalmic/otolaryngologics/dermatologics	154 (13)	2 (7)	152 (13)	0.56
Laxatives	191 (16)	6 (22)	185 (16)	0.38
Local anesthetics	39 (3)	2 (7)	37 (3)	0.22
Corticosteroid	138 (12)	6 (22)	132 (11)	0.08
Hormones/insulin	24 (2)	2 (7)	22 (2)	0.1
Aminophylline	67 (6)	0 (0)	67 (6)	0.4
Peptic ulcer drugs	111 (9)	2 (7)	109 (9)	1.0

Data are presented as n (%) unless otherwise indicated

ADEs adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

[a] One patient without cancer received an antitumor agent to treat a non-malignant condition

respiratory, 37 (25%) bone marrow suppression or cytopenia, and seven (5%) other.

4 Discussion

The rate of ADEs in pediatric patients with cancer was higher than in those without cancer—cancer patients had seven ADEs on average. Although the sample size of cancer patients was small, the overall severity of the ADEs seemed similar between cancer and non-cancer patients. While most of the ADEs for cancer patients were caused by antitumor agents, most of the fatal or life-threatening ADEs were caused by sedatives and blood products. The classes of drugs causing fatal or life-threatening ADEs seemed to differ between pediatric patients with cancer and those without.

Data on ADEs among pediatric patients with cancer are sparse. For example, Takata et al. [13] found that pediatric patients with cancer more frequently experienced ADEs and that hematology and oncology wards had a higher incidence of ADEs. In this study, while we found that

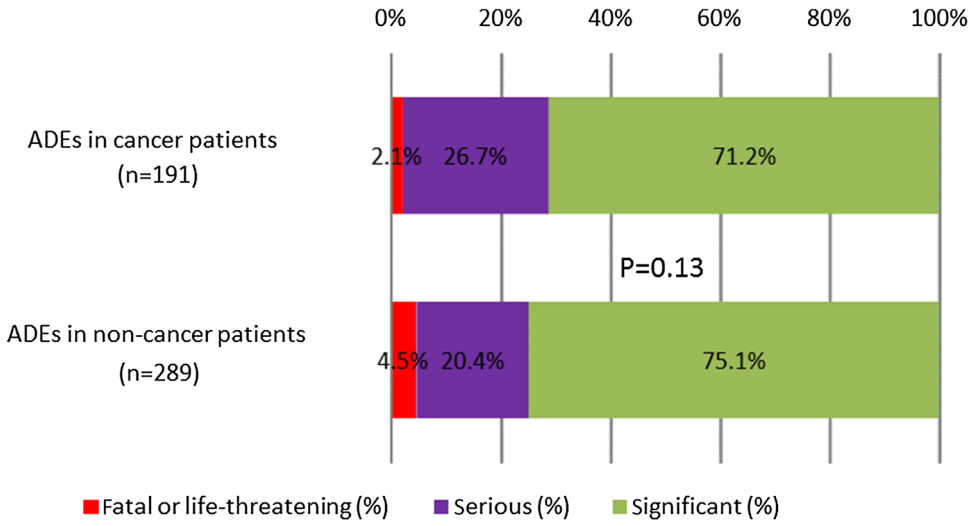

Fig. 1 Comparison of adverse drug event severity between cancer patients and non-cancer patients. *ADEs* adverse drug events

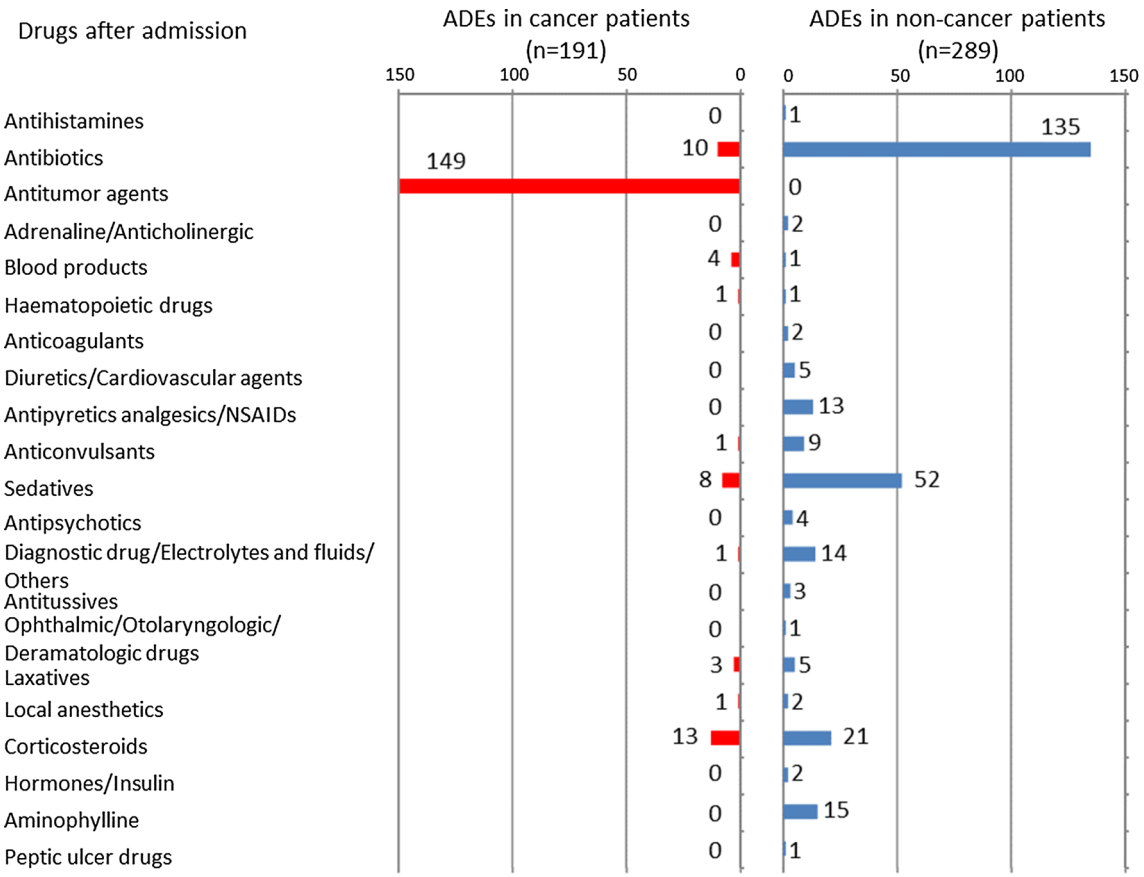

Fig. 2 Causative drugs of adverse drug events. *ADEs* adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

ADEs occurred frequently in pediatric cancer patients, the rate of fatal or life-threatening ADEs was much lower (2.1%). A systematic review of studies in pediatric patients with leukemia reported treatment-related mortality (which should be considered an ADE) of 3.6% [14], which is similar to the rate in our data. The higher incidence of all ADEs but comparable risk for fatality in the current study might be because we proactively collected all ADEs in a standard manner, and most ADEs were minor injuries.

The prevalence of ADEs by medication classes differs between settings. For example, one study in hospitalized adults found that 32% of ADEs due to antitumor agents were fatal [15]. Moreover, another study [16] in patients with unplanned cancer admissions found that 13% had

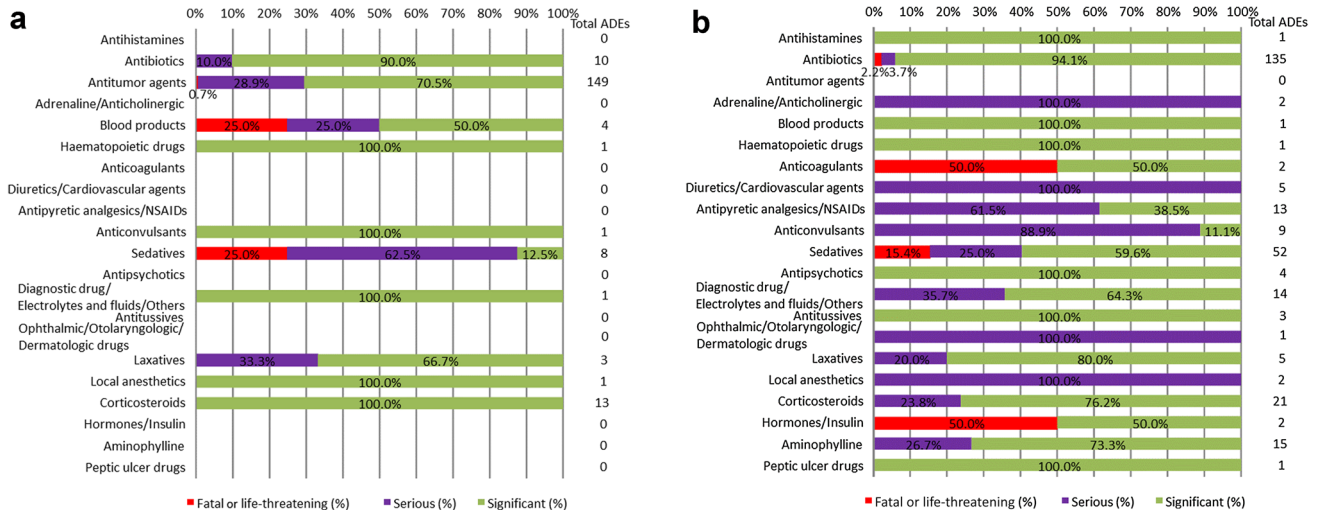

Fig. 3 Severity of adverse drug events in **a** cancer and **b** non-cancer patients. *ADEs* adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

ADEs. Furthermore, Nazer et al. [15] reported that, among oncology patients, the medications most commonly associated with an ADE requiring ICU admission were antitumor agents, analgesics, and anticoagulants. In contrast, in the current study in the pediatric setting, only one (0.7%) fatal or life-threatening ADE due to antitumor agents occurred, although the number of patients evaluated was small.

As sepsis from febrile neutropenia (FN) sometimes causes a fatal ADE, it is an important type of ADE due to antitumor agents. Admittance for FN has been reported to be 4.4 per 100 oncology admissions [16], with an annual incidence of 19.4 cases of FN per 1000 oncology admissions [17]. Because we classified such symptoms as bone marrow suppression rather than FN, the incidence of bone marrow suppression was higher, at 205 per 100 cancer patients. This provides additional evidence that antitumor agents as a class are most commonly associated with ADEs.

We must recognize that drugs with great benefit generally have a high rate of ADEs. Moreover, differences were apparent between the drug classes causing ADEs in cancer patients compared with in non-cancer patients. Such differences should be noted to assist with awareness and proper monitoring when these drugs are administered. Although the frequency of ADEs due to antitumor agents was high, the high risk for fatal or life-threatening ADEs with other drugs, namely blood products and sedatives, should also be considered for pediatric patients with cancer.

Our study has several limitations. First, the number of pediatric patients with cancer was much smaller than that without cancer, so we could not draw definitive conclusions. On the other hand, this study was conducted at a daily clinical setting, and the findings reflect real-world data. Second, we conducted this pediatric study at two tertiary care teaching hospitals. Therefore, the results are not generalizable to non-tertiary care teaching hospitals, in which most children receive medical care in Japan. Third, some ADEs may not have been noted in the charts and may thus not have been detected, potentially resulting in underestimation of ADEs. In addition, because many ADEs due to antitumor agents are well-known and noticeable, other ADEs in cancer patients might have been overlooked. However, more robust alternatives to measure ADEs have not yet been developed. Finally, the classification of ADEs seemed arbitrary, and many symptoms were difficult to classify as ADEs or other conditions. However, we determined the most likely causative drug based on the historical evidence from the literature, and this method is the best one currently available.

5 Conclusion

Pediatric patients with cancer had more frequent ADEs than did those without cancer. While most ADEs in cancer patients were caused by antitumor agents, other medications caused the greatest proportion of fatal or life-threatening ADEs. The overall severity of ADEs in patients with and without cancer was similar. Nonetheless, knowing which medication classes have higher risks for ADEs in pediatric patients with and without cancer may help providers more carefully use those medications and monitor patients, which may in turn help to minimize the impact of ADEs in pediatric patients overall.

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Compliance with Ethical Standards

Informed consent The institutional review boards of the two participating hospitals approved the study. Because all data were obtained as part of routine daily practice, the institutional review boards waived the need for informed consent.

Conflict of interest Drs. Koizumi, Ohta, Sakuma, Okamoto, Matsumoto, and Morimoto have no conflicts of interest. Dr. Bates received equity from Intensix, which makes software to support clinical decision making in intensive care; is named as co-inventor on patent no. 6029138 held by Brigham and Women's Hospital (Boston, MA, USA) on the use of decision-support software for medical management licensed to the Medicalis Corporation; holds a minority equity position in Medicalis, which develops web-based decision support for radiology test ordering; consults for EarlySense, which makes patient safety monitoring systems; has received equity and cash compensation from QPID Inc., a company focused on intelligence systems for electronic health records; has received cash compensation from CDI (Negev) Ltd., a not-for-profit incubator for health IT startups; and has received equity from Enelgy, which makes software to support evidence-based clinical decisions, from Ethosmart, which makes software to help patients with chronic diseases, and from MDClone, which takes clinical data and produces de-identified versions of it.

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Ethical approval This study was approved by all institutional review boards at all participating hospitals and was conducted in accordance with the provisions of the Declaration of Helsinki and the ethical guidelines for clinical studies in Japan.

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